FEBS Letters 585 (2011) 677–682

journal homepage: www.FEBSLetters.org

Cyclophilin D deficiency prevents diet-induced obesity in mice

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ARTICLE INFO

Article history:
Received 17 January 2011
Accepted 19 January 2011
Available online 27 January 2011

Edited by Laszlo Nagy

Keywords:
Adolescent obesity
Energy metabolism
Mitochondrial uncoupling
Permeability transition pore

ABSTRACT

Mitochondrial coupling efficiency is pivotal in thermogenesis and energy homeostasis. Here we show that deletion of cyclophilin D (CypD), a key modulator of the mitochondrial permeability transition pore, demonstrated resistance to diet-induced obesity (DIO) in both male and female mice, due to increased basal metabolic rate, heat production, total energy expenditure and expenditure of fat energy, despite increased food consumption. Absorption of fatty acids is not altered between CypD$^{-/-}$ and wild-type mice. Adult CypD$^{-/-}$ developed hyperglycemia, insulin resistance and glucose intolerance albeit resistant to DIO. These data demonstrate that inhibition of CypD function could protect from HFD-IO by increasing energy expenditure in both male and female mice. Inhibition of CypD may offer a novel target to modulate metabolism.

1. Introduction

When dietary energy is maintained at a constant level, weight gain or loss depends on the energy expenditure through exercise and other obligatory bodily functions and on the coupling efficiency. Coupling efficiency is defined as the proportion of the calories burned and oxygen consumed that is coupled to ATP synthesis. One of the mechanisms by which metabolic efficiency can be lowered is to activate futile cycles of ATP synthesis and hydrolysis. Proton leaks have been reported to account for 26% of resting energy expenditure in isolated hepatocytes and up to 50% in perfused rat skeletal muscle [1]. Although the mechanism for the proton leak is not defined, the adenine nucleotide translocase (ANT), involved in export of ATP from mitochondria, is implicated [2]. In addition, oxidative phosphorylation is uncoupled by inducible proton leak in specialized tissues such as brown fat by uncoupling proteins (UCPs) to cause adaptive thermogenesis.

Obesity is associated with diminished brown fat activity [3] and it was proposed that a malfunction of the brown-fat-specific uncoupling by UCP-1 may explain this phenomenon. Interestingly, UCP-1 gene deletion, although lacked the ability to respond to β-adrenergic stimulated thermogenesis during acclimation to cold [4], they failed to demonstrate an obese phenotype [5,6]. However, a recent report demonstrated that at thermoneutrality, the metabolic efficiency was increased in UCP-1 deficient mice and they had an obesogenic phenotype [7], rekindling the role for UCP1 in bioenergetics.

Another possible mechanism by which leakage of protons may occur is by the intermittent opening of mitochondrial permeability transition pore (MPTP). MPTP opening allows small molecules below the size of 1500 Da to pass through the inner mitochondrial membrane causing disruption of the transmembrane potential and proton gradient [8]. Cyclophilin D (CypD) is a critical component of the PTP that can modulate the permeability of the channel in response to various stress stimuli [9]. A role for MPTP in diet-induced obesity has not been investigated. We hypothesized that modulation of MPTP by CypD could be an alternate mechanism by which energy metabolism is uncoupled and adaptive thermogenesis could occur. To test, we fed HFD to CypD deficient mice and determined the effect of CypD deficiency on body weight, food intake, energy expenditure, body fat stores and glucose tolerance.

2. Results

2.1. CypD deficient mice are resistant to high fat diet-induced obesity

In order to determine the effect of CypD deficiency on energy homeostasis, we fed 6 week-old male and female cypD$^{-/-}$ mice along with age and genetically matched wild-type (WT) (B6129SF2/J) mice with either high fat (HF; 45% fat by calories,

Abbreviations: CypD, cyclophilin D; WT, wild-type; HF, high fat; RQ, respiratory quotient; MPTP, mitochondrial permeability transition pore

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0014-5793/$36.00
doi:10.1016/j.febslet.2011.01.031

4.76 kcal/g) or normal diet (ND; 10% fat by calories, 3.85 kcal/g) for a period of 19 weeks. The body weight of mice from different groups was similar at the beginning of the study. Mice from all groups were weighed weekly and quantitative data demonstrated that the rate at which body weight increased was significantly lower in HF fed CypD$^{-/-}$ male (Fig. 1A) and female (Fig. 1B) mice compared to their WT counterparts. CypD$^{-/-}$ mice appeared smaller in size compared to their WT counterparts at 17 weeks post-HF diet and a representative photograph of the male animals is shown (Supplementary Fig. S1A). These results demonstrate that both male and female cypD$^{-/-}$ mice are resistant to HF diet-induced obesity.

To understand the mechanism by which CypD deficiency protects against obesity, the body weight and fat mass, food intake, metabolic level and energy expenditure were measured in CypD$^{-/-}$ and WT mice. At 19 weeks post-HF feeding, the difference in body weight between cypD$^{-/-}$ and WT male mice was 34.6% ($n = 4$; $P < 0.01$) and female mice was 38.4% (Fig. 1C-top panel). No difference in body weight between control diet fed WT and CypD$^{-/-}$ mice was noted up to 19 weeks post-feeding. Analysis of the body composition of cypD$^{-/-}$ and WT male mice fed HF, using quantitative nuclear magnetic resonance (NMR) method, at the 19 week study's completion time point revealed that CypD$^{-/-}$ mice have significantly lower percentage of fat mass ($P < 0.01$; $n = 4$), increased water content ($P < 0.01$; $n = 4$) but no change in the percentage of lean mass compared to WT mice (Fig. 1C-bottom panel).

2.2. Food consumption is decreased in female but not in male cypD$^{-/-}$ mice

Measurement of food intake in HF-fed CypD$^{-/-}$ and WT male mice demonstrated that the cumulative food intake over a period of 17 weeks adjusted for body mass demonstrated a significant increase in both male and female CypD$^{-/-}$ mice (Fig. 2A and B, respectively). However, the average feed consumption in absolute mass and kilocalories are comparable during the HF feeding period in male CypD$^{-/-}$ and WT mice but significantly decreased in female CypD$^{-/-}$ mice on HF diet compared to their WT counterparts (Supplementary Fig. S2A and S2B). The cumulative feed efficiency (increase in body weight relative to energy intake), determined as previously described [10] was also significantly decreased in both male and female CypD$^{-/-}$ mice compared to their WT counterparts (Supplementary Fig. S2C). These data suggest that the decrease in body weight in CypD$^{-/-}$ male mice is independent of feed intake, and despite similar levels of feed consumption, CypD$^{-/-}$ male mice

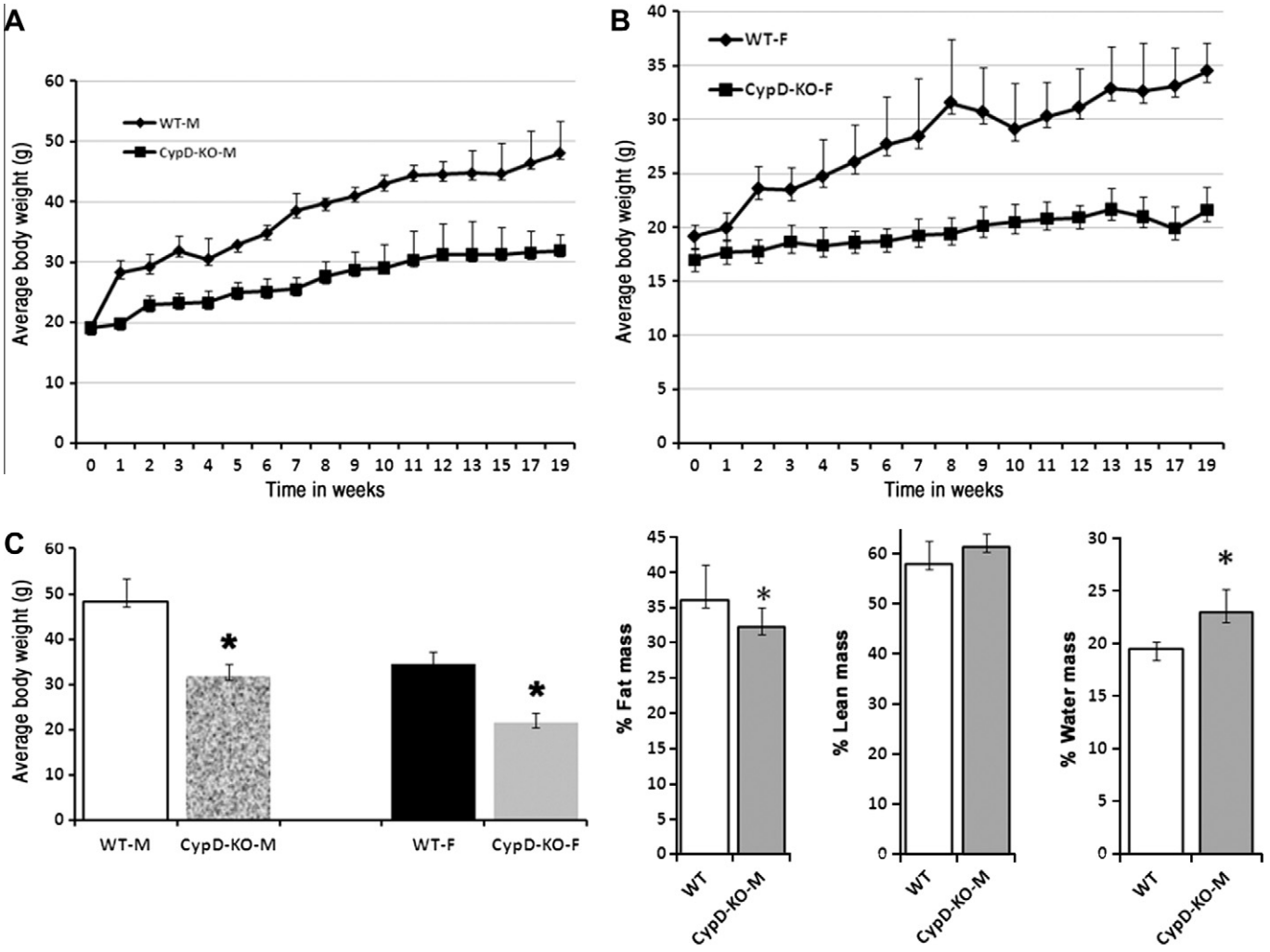

Fig. 1. (A) Average body weights of WT and CypD$^{-/-}$ male mice: ($^*P < 0.001$; $n = 6$–8) compared to WT high-fat diet fed male mice. (B) Average body weight of female mice: $^*P < 0.001$ ($n = 6$–8) compared to WT high-fat fed female mice. (C-top panel) The average body weight of WT and CypD$^{-/-}$ male mice fed HF-diet for 19 weeks. (C-bottom panel) The percentage of fat mass ($^*P < 0.01$), lean mass ($P > 0.05$) and water mass ($^*P < 0.01$) in WT and CypD$^{-/-}$ male mice fed HF-diet for 19 weeks were analyzed by the NMR method ($n = 4$ per group).

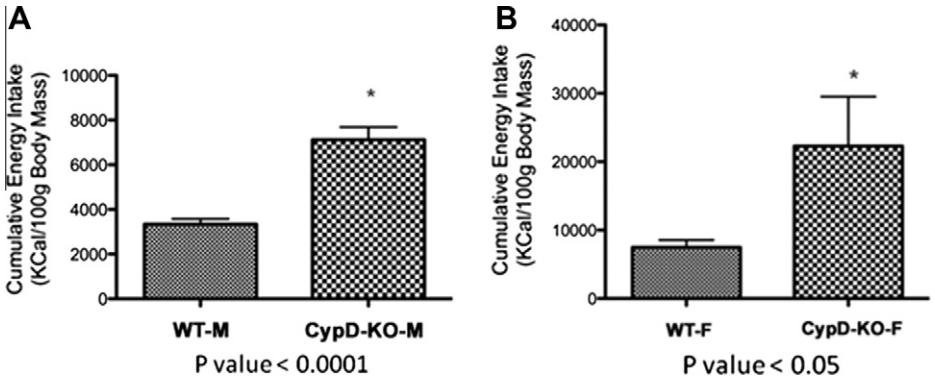

Fig. 2. (A) Cumulative energy intake adjusted for body mass in WT and CypD$^{-/-}$ male mice on HF diet for 17 weeks: $^{*}P < 0.05$ compared to WT mice on high-fat diet ($n = 8$). (B) Cumulative energy intake adjusted for body mass in WT and CypD$^{-/-}$ female mice on HF diet for 17 weeks: $^{*}P < 0.05$ compared to WT mice on high-fat diet ($n = 8$).

did not accumulate fat suggesting increased expenditure of energy possibly by uncoupling of respiration.

2.3. Food reabsorption is not altered in CypD-KO mice

In order to determine if the difference in fat absorption efficiency between WT and CypD-KO mice was due to a difference in fat reabsorption, fecal lipid output was measured directly after they were fed the HF diet for 18 weeks. The percentage of palmitate (16:0) in the fecal sample was 34.86 ± 2.358 and 27.14 ± 3.470 ($P > 0.05$; $n = 4$) in CypD-KO and WT mice, respectively. The percentage of stearate (18:0) in the fecal sample was 56.59 ± 4.488 and 50.22 ± 4.081 ($P > 0.05$; $n = 4$) in WT and CypD-KO mice, respectively. The percentage of oleate (18:1) in the fecal sample was 11.86 ± 4.488 and 12.75 ± 4.081 ($P > 0.05$; $n = 4$) in WT and CypD-KO mice, respectively. These data demonstrate that there are no significant changes in absorption of the fat content as the fecal content of fat was not altered between the groups and thus, the decreased obesity in CypD-KO mice may not due to an alteration in the fecal lipid output when maintained on a high-fat diet. Collectively, these data suggest that the resistance to DIO observed in HF-fed CypD$^{-/-}$ mice is not due to hypophagia or an alteration in the fecal lipid output.

2.4. Decreased body weight in cypD$^{-/-}$ mice is partly due to increased energy expenditure

Indirect calorimetry experiments were carried out to investigate whether the resistance to weight gain in CypD$^{-/-}$ mice is due to increased energy expenditure. CypD$^{-/-}$ mice maintained on HF diet for 19 weeks were placed in the indirect calorimeter for 24 h with unlimited access to HF diet and water. CypD$^{-/-}$ mice consistently had an increase in metabolic rate as demonstrated by an increase in oxygen consumption compared to WT mice (61.93 ± 0.35 in CypD$^{-/-}$ versus 49.39 l/kg of body weight of VO_2 in WT mice) (Fig. 3A) as well as an increase in CO_2 produced (Fig. S3A). The respiratory quotient (RQ) of 0.82 measured during the active period (dark cycle) in CypD$^{-/-}$ mice indicates that these mice used fatty acids as the main energy source while a RQ of 0.89 in WT mice indicated the use of more carbohydrates than fat as their energy source (Fig. 3B). Thus the effect of CypD deficiency on decreasing body weight and fat mass may be influenced by the decreased RQ and increase in fat oxidation. This notion is further supported by our observation that levels of circulating triglycerides and free-fatty acids were similar in both genotypes, suggesting that in CypD$^{-/-}$ mice, triglycerides were being rapidly oxidized in energy-consuming tissues. Further, analysis of the body composition of cypD$^{-/-}$ and WT male mice fed HF, using NMR also revealed that CypD$^{-/-}$ mice have significantly lower percentage of fat mass (see above). Heat (cal/h/kg) was measured for 24 h in cypD$^{-/-}$ and wt mice during the 24 h period (Fig. 3C) and was 18 144 cal/kg/h and 14 572 cal/kg/h, respectively. The mean energy expenditure (EE) was calculated separately during both light and dark cycles. CypD$^{-/-}$ mice demonstrated increased energy expenditure during both cycles.

2.5. Body temperature

The body temperature of WT and CypD$^{-/-}$ mice was measured using a rectal probe. Heat production (cal/h/kg) is a measure of caloric output and is directly proportional to metabolic rate. Both WT and CypD$^{-/-}$ male mice displayed the expected diurnal rhythm with increased heat production during the dark period ($P < 0.05$). Consistent with increase in EE, female CypD$^{-/-}$ mice had higher core body temperature (38.58 ± 0.54) compared to WT mice (38.025 ± 0.44; $n = 4$; $P = 0.181$) while male CypD$^{-/-}$ mice had core body temperature of (38.158 ± 0.54) compared to WT mice (37.58 ± 0.44; $n = 4$). The increase in body temperature of female KO mice were more prominent, a finding consistent with their complete resistance to weight gain post-HF feeding. The higher core body temperature found in CypD$^{-/-}$ mice suggests that thermogenic mechanisms to be more active in these mice to maintain homeothermy.

2.6. Normal glucose levels in cypD$^{-/-}$ mice during HF feeding

Glucose levels were monitored in CypD$^{-/-}$ mice and WT mice at several time points post-HF feeding. In both WT and CypD$^{-/-}$ mice, the levels increased gradually but were not different during the 19 week period that we studied.

2.7. Lack of insulin sensitivity and impaired glucose tolerance in CypD$^{-/-}$ HF-fed mice

In order to determine if there are any alterations in glucose homeostasis in CypD$^{-/-}$ mice, we performed an intraperitoneal glucose tolerance test (IPGTT). WT mice and CypD$^{-/-}$ mice that were fed HF-diet for 19 weeks, were fasted for 5 h followed by intraperitoneal injection with 20% D-glucose. Tail blood was collected for measurement of glucose and insulin. Intriguingly, CypD$^{-/-}$ mice had decreased ability for glucose clearance as the serum glucose levels were significantly higher over a 120 min period. Serum glucose levels were elevated at 15 min and reached even higher levels at later time points. The average values of

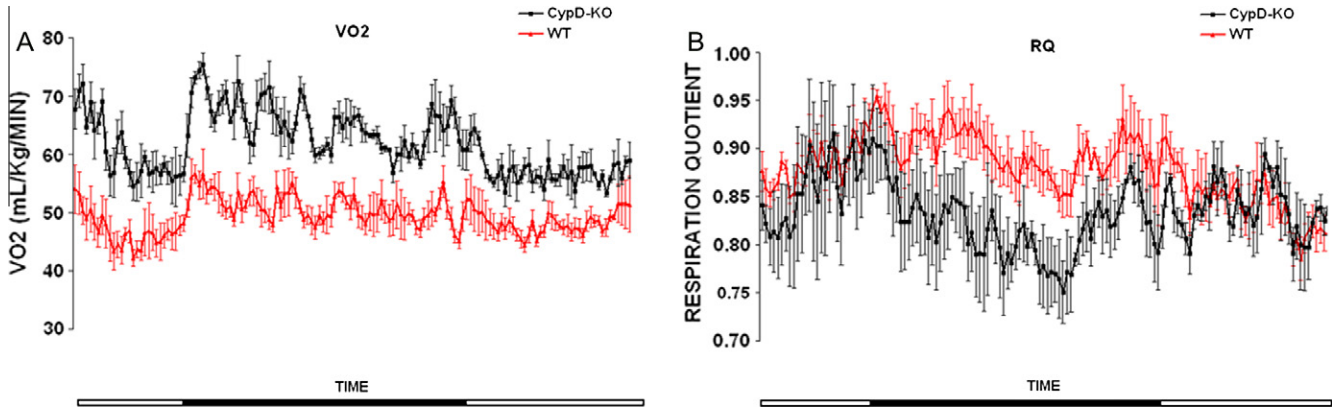

Fig. 3. (A) Comparison of the oxygen consumption for a period of 24 h for WT and CypD$^{-/-}$ mice that were fed HF diet for 19 weeks. Darkened bar area represents dark cycle. (B) Comparison of the respiration quotient for a period of 24 h for WT and CypD$^{-/-}$ mice that were fed HF diet for 19 weeks. (C) Comparison of heat dissipation by indirect calorimetry of WT and CypD$^{-/-}$ mice that were fed HF diet for 19 weeks.

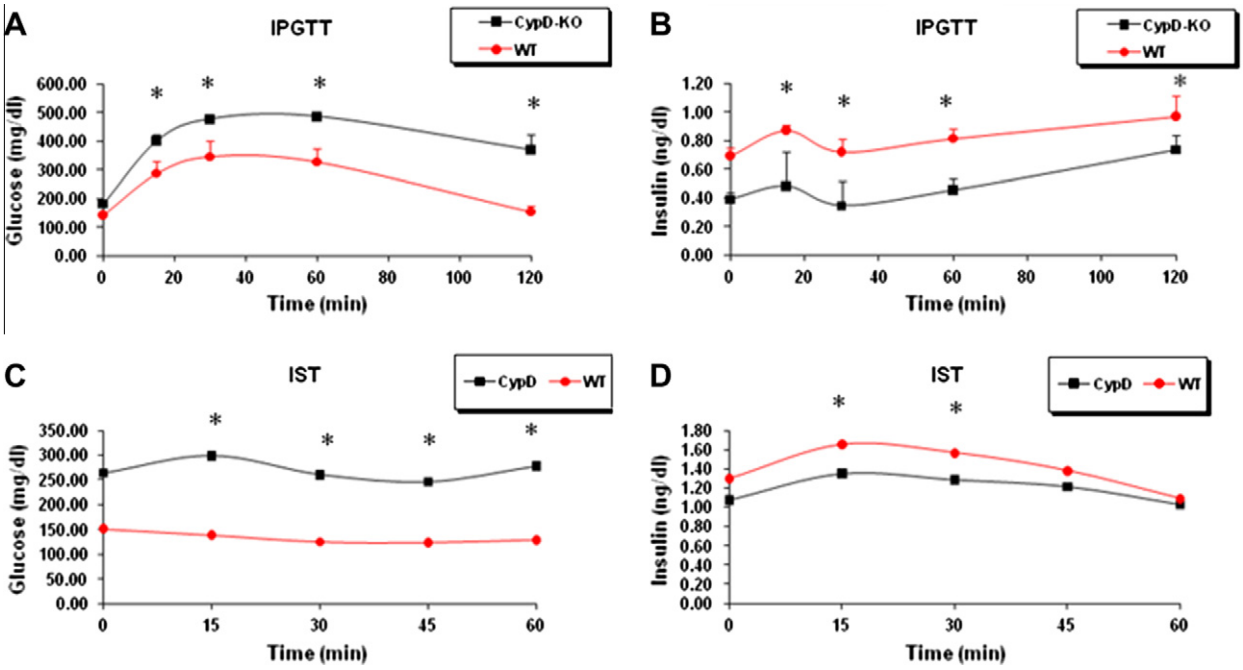

Fig. 4. (A) Comparison of glucose tolerance by IPGTT between WT and PARP-KO male mice at 19 weeks post-HF feeding: Blood glucose levels. $^{*}P < 0.05$, $n = 4$. (B) Comparison of glucose tolerance between WT and PARP-KO male mice: plasma insulin levels. $^{*}P < 0.05$, $n = 4$. (C) Comparison of insulin tolerance by insulin tolerance test (IST) between WT and CypD-KO male mice at 19 weeks post-HF feeding: blood glucose levels. $^{*}P < 0.05$, $n = 4$. (D) Comparison of insulin tolerance by insulin tolerance test (IST) between WT and CypD-KO male mice at 19 weeks post-HF feeding: plasma insulin levels. $^{*}P < 0.05$, $n = 4$.

glucose in mg/dl in WT were 144, 288, 347, 329 and 156 and in CypD$^{-/-}$ mice were 182, 402, 478, 487 and 370 at 0, 15, 30, 60 and 120 min post-glucose administration (Fig. 4A). In a separate IPGTT test, insulin measurements were performed over the 120 min post-glucose administration period. Interestingly, the plasma insulin levels were significantly lower in CypD$^{-/-}$ mice 0.392, 0.484, 0.348, 0.455 and 0.739 ng/ml in relation to WT mice 0.696, 0.875, 0.0.724, 0.0.817 and 0.973 ng/ml at 0, 15, 30, 60 and 120 min post-glucose administration (Fig. 4B). The decrease in insulin levels observed in CypD$^{-/-}$ mice, compared to WT mice at 19 weeks post-HF feeding suggests that insulin production, secretion, its maturation process may be impaired or alternatively, its degradation process may be accelerated in CypD$^{-/-}$ mice.

The ability of insulin to acutely moderate the levels of glucose or its clearance was assessed by performing insulin tolerance test (IST). At 19 weeks post-HF feeding, the ability of insulin to acutely stimulate glucose disposal in CypD$^{-/-}$ mice was significantly blunted throughout the 60 min period monitored suggesting decreased insulin sensitivity or insulin availability (Fig. 4C). The level of glucose was 278 mg/dl in CypD$^{-/-}$ mice compared to 129 in WT mice ($P < 0.05$; $n = 4$ per group) at the 60 min time point post-insulin administration. The amount of serum insulin post IST test shows that the level of insulin in CypD$^{-/-}$ mice is lower compared to that in WT mice at 0, 15, 30 and 45 min time periods post-insulin administration (Fig. 4D). This data suggests that insulin may be removed from circulation at a higher pace in *CypD*$^{-/-}$ mice compared to that in WT mice.

3. Discussion

The major factor that could contribute to the decreased body weight after high calorie intake is the imbalance in energy intake

and expenditure [11]. Quantitative data demonstrate that male HF fed CypD$^{-/-}$ mice have similar feed intake, feed efficiencies and gross energetic efficiencies compared to their WT sex-matched counterparts. These data suggest that CypD$^{-/-}$ mice waste more of the consumed energy and store less into body energy stores than WT mice. Our data also demonstrate that there are no significant changes in absorption of the fat content as the fecal content of fat was not altered between the groups. Taken together, these findings suggest that an increased energy output in CypD$^{-/-}$ male mice contributes to their resistance to the obesity phenotype.

Concurring with the decreased weight gain observed in HF fed CypD$^{-/-}$ mice, CypD deficiency increased the oxygen consumption (VO_2), as well as the CO_2 produced (VCO_2) throughout the 24 h time period that we measured. The alterations in VO_2 and in VCO_2 resulted in a decreased RQ of 0.76 compared to 0.82 in WT mice. Because about 90% of mammalian VO_2 is mitochondrial [1], increased VO_2 levels expressed per gram seen in CypD$^{-/-}$ mice are a direct reflection of increased mitochondrial oxidative metabolism. The RQ and VO_2 data from this experiment show that fat is more relied upon as mitochondrial fuel substrate in CypD$^{-/-}$ animals than in their WT controls. Thus the effect of CypD deficiency on decreasing body weight and fat mass may be influenced by the RQ, the increase in fat oxidation and physical activity.

In this study, we show that HF-fed CypD$^{-/-}$ mice compared to their WT counterparts had increased energy expenditure (EE). EE derives from thermogenesis resulting from cellular metabolic processes, including basal metabolism, adaptive thermogenesis and physical activity. Basal metabolism represents the heat production of the body in a thermoneutral environment, under resting conditions [1]. Our core body temperature measurements indicate that the basal metabolism is increased in HF-fed CypD$^{-/-}$ male and female mice, consistent with an increase in total EE and increased oxygen consumption. The higher core body temperature found in CypD$^{-/-}$ mice suggests that thermogenic mechanisms to be more active in these mice to maintain homeothermy. Because there is a significant energy cost attached to maintenance of body temperature [12], this may partially account for the increased metabolism seen in CypD$^{-/-}$ mice. Heat production (cal/h/kg) is a measure of caloric output and is directly proportional to metabolic rate. Both WT and CypD$^{-/-}$ male mice displayed the expected diurnal rhythm with increased heat production during the dark period ($P < 0.05$). Heat production per animal was increased in CypD$^{-/-}$ male mice compared to WT mice over a 24 h time period.

Adaptive thermogenesis is the process by which energy is dissipated in the form of heat in response to environmental changes such as exposure to cold and alterations in diet [11]. Under homeostatic conditions, adaptive thermogenesis is a key mechanism by which body maintains core temperature and regulates energy expenditure and its dysregulation promotes obesity [13]. Exposure of CypD$^{-/-}$ male and female mice did not result in significant changes in their core body temperature over a 6 h time period.

It is well established that central melanocortin system mediated regulation of thermogenesis is dependent on output from the sympathetic nervous system (SNS) to brown fat tissue via β-adrenergic receptors [14] and cAMP [15]. Several lines of evidence also demonstrate that agonists and antagonists of the central melanocortin system results in simultaneous activation of the SNS, brown adipose tissue (BAT) thermogenesis and uncoupling protein 1 (UCP-1) suggesting regulation of thermogenesis through a SNS-BAT-UCP-1 axis (reviewed in [13]). It remains to be delineated whether CypD deficiency has any effect on the SNS or in the expression and/or function of uncoupling proteins and in catabolic pathways that may result in reduced energy dissipation in brown fat tissue.

An important question that is raised from the results of the study pertains to the association between CypD and insulin resistance in the setting of high calorie intake in adult mice. Insulin resistance following high fat diet may involve multiple target organs including adipose tissue, liver, skeletal muscle and interactions among these three organs linking to neurogenic mechanisms [16] and/or circulating factors [17]. While increased fatty acid beta-oxidation may lower cytoplasmic lipid accumulation, increasing fatty acid beta-oxidation can decrease muscle glucose metabolism, and incomplete fatty acid oxidation has the potential to also contribute to insulin resistance [18]. The effect of CypD inhibitors on HFD-IO has not been addressed in this study. It will be of interest to determine if the global deletion of cypD that existed during the development may have influenced the development of glucose intolerance and insulin resistance after HFD in the adult CypD$^{-/-}$ mice. Pharmacological inhibition of CypD in the setting of HFD-IO may determine if its transient inhibition have similar influence on glucose intolerance and insulin resistance and thus efficacy of CypD inhibition in treating and preventing obesity and its metabolic consequences.

To conclude, our data indicate that CypD deficiency prevents diet-induced obesity by increasing energy expenditure suggesting that CypD play a central role in mitochondrial bioenergetics and development of obesity. Identification of molecular mechanisms by which CypD deficiency prevented obesity may provide potential new therapeutic opportunities to treat obesity. Developing treatment approaches to inactivate CypD function may be a promising strategy to treat patients suffering from this pathological disorder.

4. Materials and methods

4.1. Animal care and feeding studies

Breeding pairs of CypD$^{-/-}$ mice were purchased from Jackson Laboratories, Maine. CypD$^{-/-}$ mice are viable, fertile, normal in size and do not display any gross physical or behavioral abnormalities. The respective WT control mice for CypD$^{-/-}$ mice (B6129SF2/J) were purchased from Jackson Laboratories. Thirty-five- to forty-day-old male and female mice were maintained on a 12-h light/dark cycle with free access to access to either a control-diet (10% fat by calories, 3.85 kcal/g), or a HF diet (45% fat by calories, 4.76 kcal/g, Research diets Inc.). Food intake and body weight were measured weekly. All Animal studies and procedures were approved by the institutional animal care and usage committee.

4.2. Body composition analysis by NMR method

At the end of the long-term feeding study (19 weeks on the HF diet), the body composition of CypD$^{-/-}$ and WT mice was analyzed with a commercial nuclear magnetic resonance machine (Echo-MRI-100; Echo Medical Systems). Body fat and lean tissue were measured during the test.

4.3. Energy expenditure

On the same group of animals indicated above, oxygen consumption and carbon dioxide production is measured using an indirect calorimeter (AccuScan Instruments Inc.) Constant airflow (0.75 l/min) was drawn through the chamber and monitored by a mass-sensitive flowmeter. Variables provided by this measurement include VO_2, VCO_2, RQ, and HEAT [19]. To calculate oxygen consumption (VO_2), carbon dioxide production (VCO_2), and RQ (ratio of VCO_2 to VO_2), gas concentrations were monitored at the inlet and outlet of the sealed chambers.

4.4. Temperature measurements

Body temperatures were measured using a rectal digital thermometer probe (model 4600; Yellow Springs Instruments, Yellow Springs, OH).

4.5. Measurement of blood glucose

Blood was collected from fasted (12 h) mice at various time points and different assays were performed as indicated. Blood glucose was assayed with a glucometer (Hemocue glucose 201 analyzer).

4.6. Intraperitoneal glucose tolerance test (IPGTT)

At the end of the long-term feeding study (19 weeks on the HF diet), 5 h fasted mice were injected intraperitoneally with D-glucose (30% solution; 2 mg/g of body weight), and blood glucose values were determined at 0, 15, 30, 60 and 120 min post-injection. Baseline and test samples were all obtained from the tail vein [19].

4.7. Insulin tolerance tests (ITT)

ITT were performed on the same group of animals 10 days after the IPGTT test. Mice were fasted for 5 h and blood was collected for baseline glucose values. Animals were injected intraperitoneally with 0.5 mU/g insulin (100 mU/ml solution), and blood glucose values were determined at 0, 15, 30 and 60 min post-injection.

4.8. Statistical analysis

Data from long-term body weight studies and ITT and IPGTT were analyzed by two-way analysis of variance (ANOVA) with repeated measures. For comparisons of body composition measures, food intake (kcal), mean kcal/h, fasting plasma glucose, a Student's *t*-test was utilized. *P* values less than 0.05 were considered statistically significant. All values are presented as means ± S.E.M. unless otherwise specified.

Conflict of interest

The authors have declared that no conflict of interest exists.

Acknowledgement

Our thanks to the University of Cincinnati mouse metabolic phenotyping center for carrying out metabolic studies in our mice.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.febslet.2011.01.031.

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